

REMARKS

This is in response to the Official Action mailed June 16 2004 for the above-identified application. Claims 2 and 3 have been cancelled and Claim 1 has been amended as is further described below. Claims 1 and 4-6 are pending in this application.

Claims 1-6 have been rejected under 35 USC 112, first paragraph as allegedly not enabled by the specification. The Official Action takes the position that the specification does not enable the administration of "any CYP2D6 substrates... with any CYP2d6 inhibitors" (Official Action, page 2, last paragraph).

Without prejudice, and purely to expedite prosecution, Claim 1 has been amended to recite the limitation of now cancelled Claim 3, to wit, that the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof. As acknowledged by the Official Action (page 2, last paragraph), the specification is enabling for "the particular substrates or drug for CYP2D6 mediated oxidative biotransformation disclosed in claim 3."

In view of the foregoing, withdrawal of the rejection of Claims 1 and 4-6 as allegedly not enabled by the specification is respectfully requested.

Claims 1-6 have been rejected under 35 USC 112, second paragraph as allegedly indefinite for failing to include the recitation "an effective amount."

Without prejudice, and purely to expedite prosecution, applicants have amended Claim 1 to include the recitation "an effective amount." The preamble of Claim 1 has also been amended to recite that the method of the invention is a method of improving the pharmacokinetic profile of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation. It is respectfully submitted that neither amendment constitutes new matter.

In view of the foregoing, withdrawal of the rejection of Claims 1 and 4-6 as allegedly indefinite is respectfully requested.

Claims 1-6 have been rejected under 35 USC 103(a) as allegedly obvious over Sands (US 5,716,961) in view of Benet et al. (US 5,567,592) or Sandyk (US 5,470,846). The Official Action acknowledges that Sands does not disclose the subject matter of Claim 1 as amended (page 8, third paragraph). The Official Action alleges that Benet et al. at col. 2, lines 46 – col. 3, lines 25 and col. 7 teach that quinidine, channel blockers and phenothiazines are useful to increase the bioavailability of a pharmaceutical compound through the inhibition of cytochrome P450. The Official Action also alleges that Sandyk teaches that sertraline is a known SRI useful to treat neurological disorders. The Official Action concludes that it would have been obvious to a person of ordinary skill to employ (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol in combination with quinidine or sertraline (Official Action, page 9, lines 6-10).

It is respectfully submitted that the combination of (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol with a CYP2D6 inhibitor, such as quinidine or sertraline, is not obvious in view of the cited art. As a preliminary matter, to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 2142. The Official Action fails to show any such suggestion or motivation to combine Sands with either Benet et al. or Sandyk. In particular, the Official Action fails to consider that, even assuming *arguendo* that the combination of the references teaches every element of the claimed invention, without a motivation to combine, a rejection based on obviousness is improper. See *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

In addition, Applicants note that, with regard to sertraline, this compound is neither disclosed nor suggested in Benet et al. or Sands, while the teachings of Sandyk, when properly construed, relate specifically to a treatment with sertraline in conjunction with an AC pulsed magnetic field (see, e.g., the Summary of the Invention, col. 7, lines 44-54, and Claim 1 of Sandyk). Therefore, in Sandyk, the teachings of the prior art, which represent an *in re Rouffet* factors to consider when determining motivation to combine, are utterly unrelated to that of the present invention. With regard to the combination of Sands with Benet et al., even assuming *arguendo* that there is any motivation to combine the two references, it is respectfully submitted that the advantageousness of the combination of (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol with a CYP2D6 inhibitor such as quinidine is surprising and unexpected over the teachings of the two references. In particular, as shown in the enclosed Figures 3 and 4, the metabolism of "CP-A", which is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, is very significantly reduced in the presence of the CYP2D6 inhibitor quinidine. For example, even a concentration of quinidine as low as 0.1 μ M (see dark squares' points in Figure 3) is sufficient to increase the percentage of CP-A remaining after 60 minutes from about 40% to about 60%. It is respectfully submitted that the magnitude of the advantageousness of the combination of (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol with a CYP2D6 inhibitor such as quinidine exemplified in Figures 3 and 4 is not obvious to one skilled in the art based on the teachings of Sands with Benet et al., alone or in combination.

In view of the foregoing, withdrawal of the rejection of Claims 1 and 4-6 as allegedly obvious over Sands in view of Benet et al. or Sandyk is respectfully requested.

Claims 1 and 4 have been provisionally rejected as allegedly obvious under the judicially created doctrine of double patenting over Claim 1 of co-pending application Ser. No. 09/528,978. The Official Action alleges that Claim 1 of the co-pending application is drawn to the same or

substantially similar method in that it recites a combination of "a CYP2D6 substrate by administering a CYP2D6 inhibitor, quinidine" (Official Action, page 11, lines 4-8).

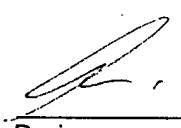
As discussed above, purely to expedite prosecution, and without prejudice, Claim 1 has been amended to recite the limitation of now cancelled Claim 3, to wit, that the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation is (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol or a pharmaceutically acceptable salt thereof. Accordingly, Claim 1 as amended, and Claim 4 dependent on Claim 1, is not obvious over Claim 1 of the co-pending application Ser. No. 09/528,978, since the compound recited in Ser. No. 09/528,978 is unrelated to (1S, 2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol. Accordingly, the subject matter of the claims in Ser. No. 09/528,978 and of the claims as amended in the instant application is clearly "the same or substantially similar."

In view of the foregoing, withdrawal of the rejection of Claims 1 and 4 as allegedly obvious over Claim 1 of the co-pending application Ser. No. 09/528,978 is respectfully requested.

In view of the foregoing amendment and remarks, allowance of all pending claims in the application is respectfully requested.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

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